REMARKS

The Office Action of October 23, 2002 presents the examination of claims 1-17 and 20-17, claims 18, 19, 28 and 29 being withdrawn from consideration following restriction.

The present paper cancels claims 1-29, substituting therefor new claims 30-36. The new claims are presented to address issues raised under 35 U.S.C. § 112, second paragraph. This method of amendment was chosen for editorial simplicity.

No new matter is added by any amendment to the claims. The term "closed circular" or "closed circular plasmid vector" recited in the new claims is a full spelling of the abbreviation "CC" that is described in the specification and figures of the present application. For example, Test Example 1 on page 28, line 18 describes "a supercoiled pDNA (CC)". It is well known to the artisan in this field that "cc" plasmid DNA is "closed circular" plasmid DNA.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-17 and 20-27 were rejected under 35 U.S.C. § 112, second paragraph; the Examiner asserted that various phrases recited in the claims rendered them indefinite. New claims 30-36

no longer include any of the phrases considered indefinite by the Examiner.

Rejections under 35 U.S.C. § 102(b)

Claims 1-4, 7-13 and 15-17 were rejected under 35 U.S.C. § 102(b) as anticipated by Szoka et al., (WO 96/40265) or by Kuma et al. (WO 96/29096). Claims 1-4, 7-13 and 15-17 are canceled, rendering these rejections moot. The present claims 30-33, 35 and 36 (as dependent on 35) recite at least one limitation that is not described in Szoka et al. or by Kuma et al. In particular, neither Szoka et al. nor Kuma et al. describe atellocollagen as a component of a composition.

Claim 34 recites a composition comprising citric acid and/or tartaric acid. Neither Szoka et al. nor Kuma et al. describe either of these ingredients as useful for formulating a composition comprising a nucleic acid.

Accordingly, the present claims are novel over Szoka et al. and the instant rejection should not be applied against the new claims 30-36.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 1, 5, 6, 11, 14 and 20-27 under 35 USC § 103 as being unpatentable over Szoka et al. in view of Fujioka et al. This rejection is respectfully traversed as applied to the present claims. Reconsideration and withdrawal thereof are requested.

Applicants submit that the Examiner fails to establish *prima facie* obviousness of the claimed invention. The deficiencies of the disclosure of Szoka et al. in describing the present invention are explained above. Fujioka does not remedy these deficiencies.

The present invention provides a formulation that retains or stabilizes the primary structure of closed circular plasmid vectors (referred to as pDNA in the specification of the present application). Although Fujioka does describe the use of atelocollagen and citric acid as stabilizing agents, Fujioka et al. describes the stabilizing of proteins, not pDNAs. Thus, the combination of Fujioka with Szoka in the manner suggested by the Examiner does not result in the present invention.

Furthermore, there is no motivation provided by the references or by the state of the art to combine the references in the manner suggested by the Examiner. As explained below, proteins and pDNAs are quite different each other in terms of their physico-chemical

properties. Accordingly, the procedures to stabilize proteins would not necessarily be applied by the skilled artisan seeking to stabilize pDNAs.

It is known in the art that closed circular plasmid vectors form a supercoil. In the creation of a closed circular plasmid vector from a linear DNA double helix, an end of the helix is bound to the other end that is partially rewound and relaxed. After the closed circular plasmid vector is formed by binding the ends, the rewound part tends to return to type B double helix, thus putting a distortion on a plasmid vector that has been circularly closed. This distortion results in supercoiling of the plasmid vector. Supercoiled plasmid vectors have a higher level of internal energy from the distortion. Thus, the cleavage of either or both of the double strands of the supercoiled plasmid vectors results in relaxed (open circular) plasmid vectors or linearized DNAs having a lower energy.

It has been known that when closed circular plasmid vectors that are in supercoiled form are lyophilized, the proportion of plasmid that is relaxed and linearized increases compared to the proportion of closed circular plasmid vectors. As shown in the Test examples and the figures in the present application, lyophilization of closed circular plasmid vectors without any

atelocollagen or other ingredient according to the present invention results in a high proportion of relaxed plasmid vectors and/or linearized DNAs (referred to as "fragmented pDNA (CC)" in the specification).

On the other hand, denaturation of proteins on lyophilization is caused by the change of higher structure of proteins that results from removal of free water, and it is rare that the peptide bound is cleaved. It is known that additives such as trehalose and raffinose that keep the glass (amorphous) state, instead of free water in proteins, contribute greatly to stabilization of the higher structure of proteins. Also, it is known that glucose, lactose and sucrose, all of which are less effective in hydration properties and are crystallized in proteins, contribute only slightly, if at all, to the stabilization of proteins.

The difference between the mechanisms of protein denaturation and the plasmid vector degradation upon lyophilization is self-evident to those skilled in the art and explains why the skilled artisan would not look to Fujioka to provide answers to the problem of stabilizing CC plasmid DNA upon lyophilization.

Furthermore, the present invention provides experimental results that are not expected by one of ordinary skill in the art who would read Szoka and Fujioka.

For example, the data in Figures 15 and 17 in the present application show that glucose and lactose (which contribute only slightly to protein stabilization) are significantly effective to stabilize plasmid vectors. Furthermore, the data in Table 3 on page 32 of the specification show that certain amino acids and the bidentate carboxylic acids citric acid and tartaric acid are unexpectedly effective in stabilizing the CC form of plasmid DNA.

As the Examiner fails to establish *prima facie* obviousness of the claimed invention over the cited references, the instant rejection should not be applied to the present claims. The instant rejection is also inappropriate because the invention provides experimental results not expected by the skilled artisan who might read the cited references.

Applicants submit that the present application well describes and claims patentable subject matter. The favorable action of withdrawal of the standing rejections and allowance of the application is respectfully requested.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 1-29 have been canceled.

Claims 30-36 have been added.